Chapter D

Preterm Labor & Premature Rupture of Membranes

slide 1

William Sayres, M.D.

Published June 2011

OBJECTIVES

slide 2

At the end of this lecture, participants will be able to:

- Define preterm labor (PTL) and premature rupture of membranes (PROM) and describe their significance.
- List risk factors associated with PTL and PROM.
- Outline initial evaluation of PTL and PROM.
- Describe management of PTL and PROM.
- Discuss neonatal group B streptococcal (GBS) prevention strategies.

INTRODUCTION

Previous preterm delivery (PTD) is the most important historical risk factor for subsequent PTD. Other important antenatal risk factors include multiple gestation, bacterial vaginosis, and short cervix. In a patient presenting with preterm contractions, cervical length on transvaginal ultrasound or a fetal fibronectin test can be used to help assess the risk of preterm delivery. Progesterone may be used to decrease the likelihood of preterm delivery in patients with a prior preterm delivery or a short cervical length on ultrasound. Administration of antenatal corticosteroids remains our most important intervention to improve perinatal outcomes in women presenting with preterm labor (PTL). Tocolytic agents may delay preterm delivery allowing time to administer steroids or transfer to facilities with a Neonatal Intensive Care Unit (NICU). Management of preterm premature rupture of membranes (PPROM) may include administering antibiotics, antenatal corticosteroids, or labor induction based on the gestational age at presentation. Management of premature rupture of membranes (PROM) at term includes early induction/augmentation of labor.

EPIDEMIOLOGY

slide 3

The United States' incidence of preterm delivery (PTD), defined as occurring before 37 weeks' gestation, was 12.3 percent in 2008.[1] About 40 to 45 percent of preterm deliveries are the result of spontaneous preterm labor with intact membranes. Twenty-five to 30 percent are associated with preterm premature rupture of the membranes. The remaining 30 to 35 percent of preterm deliveries are the result of delivery by labor induction or cesarean section for medical indications such as severe preeclampsia, placental abruption, or intrauterine growth restriction.[2]

slide 4

The incidence of PTD increased 20 percent from 1990 to 2006. This increase has been associated with a rise in multiple gestations and increased indicated late preterm deliveries (between 34 and 36 weeks' gestation). The rate has fallen from 12.8 percent in 2006 to 12.3 percent in 2008; perhaps due to efforts to decrease the proportion of elective inductions and cesarean deliveries occurring

before 37 weeks.[1] The use of assisted reproductive technology (ART) has resulted in an increase in multiple gestations; singleton pregnancies conceived with ART are also associated with shorter gestations.[3] Although infant mortality rates increase significantly below 32 weeks,[4] late preterm delivery, defined as 34 to 36 weeks' gestation, is nevertheless responsible for significant morbidity, including the majority of NICU admissions.[5] Despite the increase in the rate of PTD, the rates of infant and neonatal mortality in the US have fallen steadily.[4] At least some of the continuing decrease in perinatal mortality may be attributed to medically indicated preterm delivery.[6]

RISK FACTORS FOR PTD

Up to 50 percent of extremely preterm deliveries occur in pregnancies with no known risk factors.[7]

slide 5

Maternal characteristics: African-American race is associated with increased rates of PTD and of extreme PTD in particular.[1] Short interpregnancy interval (< six months) increases the risk of PTD by 1.4 (95%CI 1.24 to 1.58).[8] Maternal nutritional status and, in particular, pre-pregnancy body mass index (BMI) of < 20 increases the odds of PTD by 3.96.[9] Pregnancies, both multiple and single gestations, resulting from assisted reproductive technology have higher rates of PTD.[10]

Maternal psychological and social stress, physically strenuous work and lack of social support have been related to PTD.[2] Physical abuse was associated in one study with an overall risk (OR) for PTD of 3.14 (CI 2.00 to 4.93).[11] Maternal exposure to environmental pollutants such as tobacco smoke and lead, as well as to air pollution, increases the risk of PTD.[12] Maternal cigarette smoking has a modest association with PTD; smoking 10 to 20 cigarettes has a relative risk (RR) of 1.2 to 1.5 and more than 20 cigarettes per day a relative risk of 1.5 to 2.0.[13] Smoking has a dose-dependent effect on incidence of PTD as well as gestational age at delivery.[14] History of cervical cone biopsy or loop electrosurgical excision procedure for cervical intraepithelial neoplasia increases the relative risk for PPROM by 2.7 to 1.9 respectively.[15]

History of preterm delivery is the most important identifiable risk factor for recurrent PTD and defines a high-risk pregnancy in the majority of research on preventive interventions. In general the risk is increased by a factor of 2.5. Risk increases with shorter penultimate gestations and number of previous preterm deliveries.[16,17] Women with a prior indicated preterm delivery are not only at increased risk for a subsequent indicated PTD, but also for subsequent spontaneous PTD.[18] Multiple gestation is one of the strongest predictors for preterm delivery with the majority of twin pregnancies delivering less than 37 weeks due to spontaneous preterm labor and medical indications for delivery.[19] Twelve percent of twin, 36 percent of triplet and 60 percent of quadruplet pregnancies will deliver prior to 32 weeks.[20]

Inflammation is one of the primary etiologic pathways to preterm labor (PTL). Infection may be the cause of the majority of extremely preterm deliveries.[21] Bacterial vaginosis (BV) increases the risk of PTD (OR 2.19; 95% CI 1.54 to 3.12) and spontaneous abortion (OR 9.91; 95% CI 1.99 to 49.34). Women screened and found positive for BV at less than 16 weeks' gestation had an even higher likelihood of PTD (OR 7.55; 95% CI 1.80 to 31.65).[22] Asymptomatic bacteriuria, possibly as a precursor to pyelonephritis, increases risk for PTD.[23] Sexually transmitted infections such as chlamydia, gonorrhea, and syphilis are all associated with increased risk for PTD.[2] Non-genitourinary infection has also been linked to subsequent preterm delivery. Periodontal infection doubles the risk for PTD.[24]

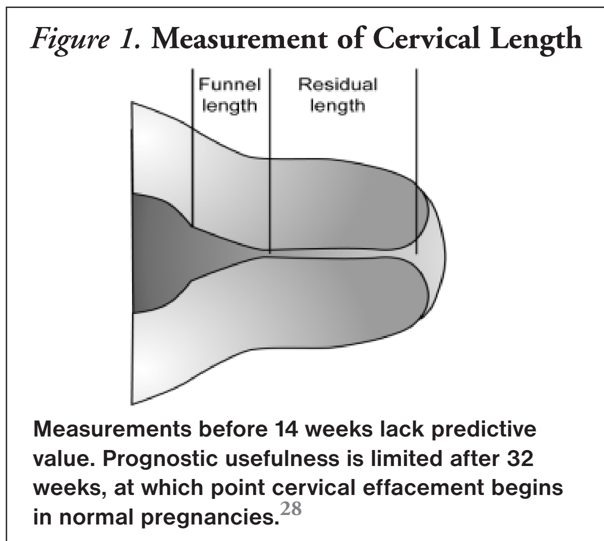
Genital Mycoplasma spp and Ureaplasma urealyticum are the most commonly identified microorganisms in the amniotic cavity in women having preterm labor.[2] Organisms theoretically ascend from the vagina and cervix before 20 weeks' gestation when membranes become tightly applied to decidua.[2] Inflammatory mediators (such as cytokines and TNF-alpha) may play a role in initiating labor. Some women may be genetically predisposed to PTD associated with infection. The TNF-alpha allele 2 gene, for instance, doubles the risk of PTD associated with BV.[25]

slide 6

Uterine contractions increase the likelihood of preterm delivery. In a study of 306 women with 34,908 hours of monitoring, increased uterine contractions were associated with preterm delivery; however, there was not a threshold frequency of contractions that effectively identified a high-risk group.[26]

Short cervical length and funneling of the cervix on ultrasound indicate increased risk for preterm delivery. Proper technique for ultrasonic cervical measurement is described in several papers.[27,28] Figure 1 demonstrates the ultrasonic parameters as depicted by Iams.[27]

***Figure 1.* Measurement of Cervical Length**



Measurements before 14 weeks lack predictive value. Prognostic usefulness is limited after 32 weeks, at which point cervical effacement begins in normal pregnancies.[28]

***Figure 2.* Cervical Length and Relative Risk of Preterm Delivery**

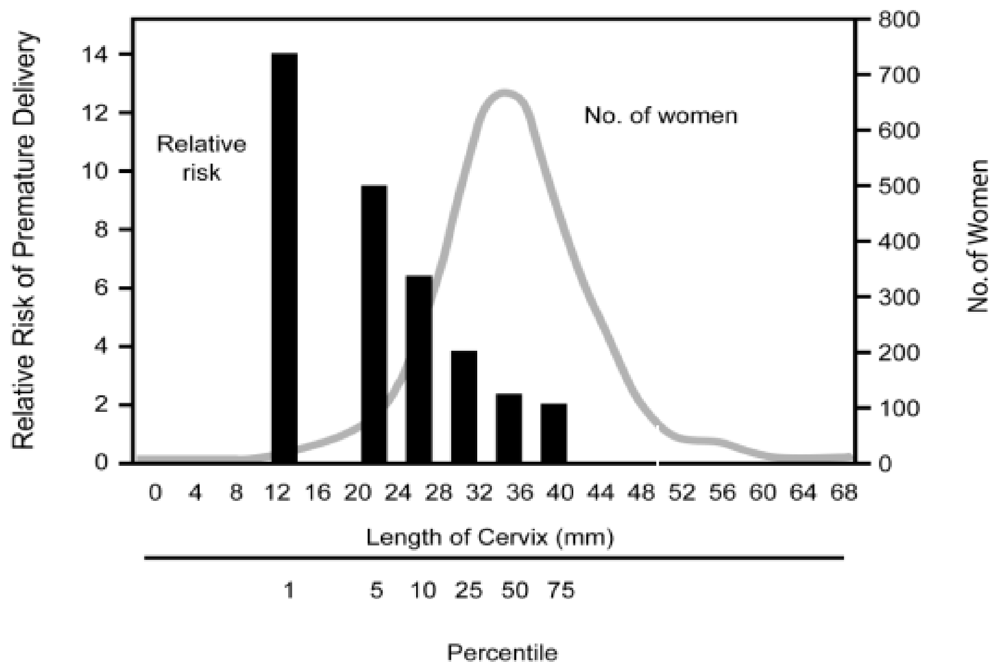


Figure 2 summarizes findings from a study of cervical lengths of 2915 women at 24 weeks' gestation. The bars represent relative risk of PTD before 35 weeks for a given cervical length. The bell-shaped graph reflects the distribution of cervical lengths. Relative risk of PTD increases as the cervical length shortens. In general, a short cervix is considered less than 30mm.[29]

Copyright permission obtained by the Massachusetts Medical Society, publishers of the New England Journal of Medicine.

Figure 3. **Sensitivity, Specificity, Positive and Negative Predictive Values of Ultrasound Cervical Length Measured at 24 and 28 Weeks in Asymptomatic Low-risk Patients for Delivery at Less than 35 Weeks**[29]

	Cervix at 24 weeks (incidence of PTD at < 35 weeks 4.3 percent)			**Cervix at 28 weeks** (incidence of PTD at < 35 weeks 3.3 percent)		
Cervical Length (mm)	≤ 20	≤ 25	≤ 30	≤ 20	≤ 25	≤ 30
Positive Predictive Value (%)	25.7	17.8	9.3	16.7	11.3	7.0
Negative Predictive Value (%)	96.5	97.0	97.4	97.6	98.0	98.5

Table 1. **Risk Factors for Preterm Delivery (PTD)**

- African-American race
- Interpregnancy interval < 6 months
- Low pre-pregnancy BMI
- History of PTD
- Multiple gestation
- Vaginal bleeding caused by placental abruption or placenta previa
- Polyhydramnios or oligohydramnios
- Maternal abdominal surgery
- Maternal medical disorders
- History of cervical cone biopsy or LEEP
- Uterine anomalies
- Maternal psychological or social stress
- Smoking
- Cocaine or amphetamine use
- Infection:
  - Intrauterine
  - Bacterial Vaginosis
  - Chlamydia
  - Trichomonas
  - Periodontal disease
- Uterine contractions
- Short cervix

slide 7

PREVENTION OF PTD

Prevention of PTD has been the focus of intense research for the last several decades. Antenatal progesterone has shown promise in recent trials. Screening and treatment of bacterial vaginosis has been less successful historically, although better results are apparent with earlier screening, better choice of subjects and choice of antibiotic. Cervical cerclage continues to be used in certain populations.

ANTENATAL PROGESTERONE

The mechanisms by which progesterone prevents PTL include reduction of gap junction formation, oxytocin antagonism, maintenance of cervical integrity and anti-inflammation.[30]

In women with a history of PTD, antenatal progesterone reduced the risk of subsequent PTD at both < 37 and < 34 weeks,[31,32] although these results are tempered by one large study which did not demonstrate improvement in pregnancy outcome.[31] One study demonstrated decreased rates of neonatal necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen.[33] A meta-analysis supports the benefit of progesterone supplementation in decreasing the likelihood of preterm delivery in high-risk women with a relative risk of birth at < 34 weeks of 0.15, and at < 37 weeks 0.8.[32] In normal-risk women at a median of 22 weeks' gestation with a cervical length of < 15 mm, treatment with vaginal progesterone was associated with a relative risk of 0.56 for delivery before 34 weeks.[34] Progesterone does not improve the outcome in twin pregnancy.[35]

Table 2. **Progesterone Formulation and Dosage for the Prevention of PTD**[36]

Formulation	Dosing	Indication
17 alpha-hydoxyprogesterone caproate	250 mg IM weekly from 16 to 20 weeks through 36 weeks	Prior preterm delivery[33]
Progesterone capsule	100 mg vaginally HS from 24 to 34 weeks	Prior preterm delivery[37]
Progesterone capsule	200 mg vaginally HS from 20 to 34 weeks	Cervical length < 15 mm[34]

A meta-analysis demonstrated 0.29 RR of PTD < 37 weeks' gestation and 0.30 RR of neonatal respiratory distress syndrome. The American College of Obstetricians and Gynecologists recommends that progesterone supplementation be offered to patients with a history of PTD as well as for those with serendipitously noted ultrasonic cervical length < 15 mm.[38]

slide 8

TREATMENT OF INFECTION

Screening for bacterial vaginosis (BV) in asymptomatic low-risk women remains controversial. Three studies screened asymptomatic, low-risk women for BV early in the second trimester and treated with clindamycin (vaginally in two and orally in one). In all three studies, the treated women had lower rates of PTD and also less late second-trimester miscarriages.[39,40,41] A Cochrane analysis based on only one of the above studies concluded that screening and treating asymptomatic women for lower genital tract infections reduced the incidence of delivery before 37 weeks.[41] In contrast, the U.S. Preventive Services Task Force recommends against screening for BV in low-risk women and concludes that evidence is insufficient to recommend for or against screening for and treating BV in high-risk patients.[42]

Although most studies use criteria based on gram stain, most clinicians will rely on Amsel's[43] criteria for diagnosis of BV.

slides 9

Table 3. **Amsel's Criteria for Diagnosis of Bacterial Vaginosis**

Diagnosis requires three of four findings
Homogenous, white, non-inflammatory discharge that smoothly coats the vaginal walls
Presence of clue cells on microscopic examination
pH of vaginal fluid > 4.5
Fishy odor of vaginal discharge before or after addition of 10 percent KOH

Clindamycin was used for the treatments of bacterial vaginosis in the three studies cited above with either 300 mg by mouth twice daily for five to seven days or two percent vaginal cream nightly for three to six days. Vaginal clindamycin treatment is not included in the recommended treatment regimes from CDC listed below.

Table 4. **CDC Recommendations for Treatment of Bacterial Vaginosis in Pregnancy**[44]

Metronidazole	500 mg orally twice a day for seven days
Metronidazole	250 mg orally three times a day for seven days
Clindamycin	300 mg orally twice a day for seven days

CERVICAL CERCLAGE

Although premature cervical change might be the result of a structurally weak cervix, shortening might also be the result of endocrine, paracrine or inflammatory processes.[30] Infection, for example, is associated with up to 51 percent of patients presenting with cervical insufficiency.[25] Cerclage specifically addresses structural deficits in the cervix and would not necessarily be as effective for other processes such as infection. Meta-analysis of 2175 patients given prophylactic cervical cerclage demonstrated a small reduction in births under 33 weeks' gestation, and was associated with mild pyrexia, increased use of tocolysis and hospital admissions and did not improve neonatal outcomes.[45]

SMOKING CESSATION, ASYMPTOMATIC BACTERIURIA AND OTHER INTERVENTIONS FOR THE PREVENTION OF PTD

In a large observational study in Sweden, women with a previous preterm delivery and who smoked during that pregnancy had a decreased risk of subsequent PTD if they did not smoke.[14] Smoking cessation programs reduce the relative risk of PTD (0.84 CI 0.72 to 0.98).[46] Interventions for smoking cessation are not equally effective, nor are they always transferrable to different settings. Programs using rewards plus social support were most effective.[46]

Although associated with PTD, screening for and treating asymptomatic bacteriuria did not reduce the incidence of PTD. Incidences of pyelonephritis and low birth weight were decreased.[13]

Risk of PTD is not improved with regular nursing contact,[47] periodontal care,[48] or nutritional supplementation.[49]

slide 10

ASSESSMENT OF THE SYMPTOMATIC PATIENT

The following section describes initial assessment of the patient presenting with premature contractions. Goals include assessment for rupture of membranes, assessment for infection, determination of likelihood of preterm delivery. A protocol for evaluation is listed below.

Table 5. **Assessment of the Patient Presenting with Premature Contractions**

Are the membranes ruptured?	History Leakage of fluid from cervical os on sterile speculum exam Nitrazine reaction of fluid Ferning of fluid Ultrasound for oligohydramnios Amnioinfusion of indigo carmine (if above tests are nondiagnostic)
Is infections present?	Group B Streptococcus carrier status Sexually transmitted infection status Urinary tract infection Chorioamnionitis, possibly subclinical
What is the likelihood that the patient will delivery prematurely?	Single-dose terbutaline Fetal fibronectin Ultrasound cervical length

slide 11

ARE THE MEMBRANES RUPTURED?

Sterile speculum assists in evaluation of membrane integrity and facilitates collection of fetal fibronectin (fFN) sample. Direct observation of amniotic fluid leaking from the cervical os is diagnostic of ruptured membranes. Gentle fundal pressure or having the patient cough during the exam may facilitate leakage. Prolonged recumbence of the patient suspected to have ruptured membranes may lead to pooling of fluid in the vaginal vault.[50] Amniotic fluid when allowed to air dry on a slide will demonstrate ferning or arborization. A false-positive test for ferning is possible if cervical mucous is inadvertently tested. The pH of the normal vaginal environment is 4.5 to 6.0 whereas the pH of amniotic fluid is 7.1 to 7.3 and will change the color of nitrazine paper from orange to blue. Accuracy of the ferning test for diagnosis of ruptured membranes is 84 to 100 percent and the nitrazine reaction 87 to 97 percent.[51] Rupture of membranes may be diagnosed with a rapid slide test for placental alpha microglobulin-1 protein in cervicovaginal discharge. Two studies of 203[52] and 184[53] patients demonstrated strong performance as noted in Table 6 below.

Table 6. **Performance of Placental Alpha Microglobulin-1 Protein Assay in Diagnosis of ROM**

Study	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cousins et al. (n=203)[52]	98.9 percent	100 percent	100 percent	99.1 percent
Park et al. (n=184)[53]	98.7 percent	87.5 percent	98.1 percent	91.3 percent

Oligohydramnios on ultrasound supports diagnosis of rupture of membranes.[50]

IS INFECTION PRESENT?

slide 12

A high index of suspicion for infection is reasonable given the close association with PTD. Evaluate prematurely contracting patients for sexually transmitted infections, urinary tract infection and bacterial vaginosis. Unless recently tested for GBS, take a vaginal/rectal culture. Subclinical chorioamnionitis, infection without the classic findings of fever, uterine tenderness, foul-smelling discharge and maternal tachycardia, may be present.[54]

WHAT IS THE LIKELIHOOD OF PTD?

slide 13

The classic definition of labor is regular uterine contractions accompanied by the descent of the fetal presenting part and progressive dilatation and effacement of the cervix. Labor may also be defined as cervical effacement of 80 percent, or dilatation of 2 cm in the presence of regular uterine contractions. Use of regular uterine contractions as the sole criterion for diagnosis is associated with a 40 to 70 percent false-positive rate.[55] In one observational study, 38 percent of women presenting to Labor and Delivery with preterm contractions went on to deliver during that admission.[56] Early diagnosis of preterm labor, in spite of these difficulties, increases the ability to transfer a laboring mother to a facility with a neonatal intensive care unit, administer glucocorticoids and initiate prophylactic treatment of GBS.[27]

slide 14

Triaging tools available to the clinician include a single dose of subcutaneous terbutaline, the fetal fibronectin (fFN) test and cervical ultrasound. Abolishment of contractions with a single subcutaneous 0.25 mg dose of terbutaline decreased time to discharge from five to four hours when compared to observation alone.[57]

slide 15

Fetal fibronectin testing is most useful for its negative predictive value and may be used between 24 and 34 weeks' gestation. Oncofetal fibronectin is a placental glycoprotein and a major component of the chorio-decidual extracellular matrix. The negative predictive value of the fFN assay is greater than 99 percent for delivery within 14 days. The positive predictive value is 13 to 30 percent for delivery in seven to ten days for symptomatic patients.[58] The test should not be performed when there is active vaginal bleeding, or when intercourse, digital vaginal examination, or endovaginal ultrasound has occurred in the preceding 24 hours as these can yield a false positive test result.[59]

slide 16,17

Although large prospective studies are not available, in one study only one patient out of 335 with a cervical length > 30 mm delivered within seven days.[60] In patients presenting with preterm contractions, an ultrasound cervical length of > 30 mm would rule out PTL.[27] Establishing a threshold cervical length at which a patient is at increased risk is more problematic.[61] Table 7 demonstrates likelihood of delivery at different cervical lengths stratified by fFN result. Cervical length < 15 mm indicates high likelihood of PTD regardless of fFN result. In the 'grey zone' of 15 to 30 mm, fFN result has a much greater impact on likelihood of delivery and therefore is more useful in decision-making.[62]

Table 7. **Use of fFN result on Likelihood of Delivery Within Seven Days at Different Ultrasound Cervical Lengths**[62]

Cervical Length (mm)	fFN	Delivery Within seven days
≥ 30 mm	+	7.1 percent
≥ 30 mm	–	2.2 percent
≥ 15 mm, < 30 mm	+	22 percent
≥ 15 mm, < 30 mm	–	5 percent
≤ 15 mm	+	75 percent
≤ 15 mm	–	36 percent

slide 18

MANAGEMENT OF PRETERM LABOR

Once preterm labor has been diagnosed, only three antenatal interventions have been demonstrated to improve outcome: delivery at a facility with a level III nursery, administration of corticosteroids and antibiotic prophylaxis of neonatal group B streptococcal infection.

slide 19

ANTENATAL CORTICOSTEROID (ACS) TREATMENT

Treatment with antenatal corticosteroids decreases neonatal death and morbidity as listed in the table below.[63]

Table 8. **Effect of ACS on Fetal Outcomes in PTL**[63]

Outcome	RR (95 percent CI)
Neonatal death	0.69 (0.58 to 0.81)
Respiratory distress syndrome	0.66 (0.59 to 0.73)
Intraventricular hemorrhage	0.54 (0.43 to 0.69)
Necrotizing enterocolitis	0.46 (0.29 to 0.74)
Respiratory support, intensive care admissions	0.80 (0.65 to 0.99)
Systemic infections in the first 48 hours of life	0.56 (0.38 to 0.85)

Treatment with antenatal corticosteroids does not increase risk of maternal death, chorioamnionitis or puerperal sepsis.[63] Antenatal corticosteroid use is effective in women with premature rupture of membranes and pregnancy-related hypertension syndromes.[63] A single course is recommended between 24 and 34 weeks; gestation.[64] The optimal effects of ACS appear to wane after a week; however, the use of repeat courses for women who remain undelivered and at risk for PTD remains controversial due to possible adverse neonatal effects of repeat courses.[65] A single 'rescue course' of ACS prior to 33 weeks' gestation improved fetal respiratory outcomes in one study.[66] Other studies have not demonstrated improved outcomes with weekly courses of ACS[67] while showing an increase in cerebral palsy at two to three years of age.[68] Doses of corticosteroids are noted on the next page.

Table 9. **Antenatal Corticosteroids for Fetal Maturation**

Corticosteroid	Dosage
Betamethasone	Two doses of 12 mg IM twice given 24 hours apart
Dexamethasone	Four doses of 6 mg given IM every six hours[63]

TOCOLYSIS

slide 20

The goal of tocolysis is to delay delivery to allow time for maternal transfer if necessary, ACS and neonatal GBS prophylaxis. Since preterm labor may be the result of infection, decidual thrombosis, or physiologic stress leading to activation of the fetal adrenal axis, prolongation of the pregnancy may be prolonging fetal exposure to a potentially hostile environment.[30]

Nifedipine decreases the likelihood of delivering within seven days (RR 0.76; 95 % CI 0.60 to 0.97) and before 34 weeks (RR 0.83; 95% CI 0.69 to 0.99). Fetal outcomes (respiratory distress syndrome (RR 0.63; 95% CI 0.46 to 0.88), necrotizing enterocolitis (RR 0.21; 95% CI 0.05 to 0.96), and intraventricular hemorrhage (RR 0.59; 95% CI 0.36 to 0.98) are improved and maternal side effects are minimal.[69] Following cessation of labor, maintenance therapy (based on one trial) does not improve outcome.[70] Meta-analysis of randomized trials demonstrates that ***betamimetics*** are effective in delaying delivery for 48 hours. Fetal outcomes were not improved in this analysis. Maternal side effects were significant. Fetal tachycardia was also noted.[71] In 2011, the FDA warned against using terbutaline for over 48 to 72 hours for treatment of preterm labor or any use of oral terbutaline to prevent preterm labor.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the likelihood of delivery at > 37 weeks and average gestational age at delivery (weighted mean difference 3.53 weeks) with low maternal side effects.[72] Early concerns about potential neonatal side effects from indomethacin[73] are allayed by a subsequent meta-analysis and may be related to the role of infection, especially in very preterm labor.[74] According to one decision analysis, prostaglandin inhibitors may be the optimal first line agent for preterm labor before 32 weeks' gestation.[75] Another consideration might be the presence of polyhydramnios, in which case prostaglandin inhibitors would be expected to decrease amniotic fluid volume. Because of risk of premature closure of the ductus arteriosus, NSAIDs should not be used for more than 48 hours.[76]

In spite of widespread use[77] and a theoretical basis for therapeutic effect, studies of ***magnesium sulfate*** for tocolysis fail to demonstrate either prolongation of pregnancy for 48 hours nor improvements in fetal outcome.[78,79] The Cochrane analysis found magnesium sulfate for tocolysis to be ineffective. The risk of death (fetal and pediatric) was higher for infants exposed to magnesium sulfate (RR 2.82; 95% CI 1.2 to 6.6) based on seven trials (n=727).[79] Placebo controlled trials show lack of effect and trials controlled with other classes of tocolytics (including CCBs) show no differences in outcome.[78,79] Several trials of neuroprotection have demonstrated that magnesium sulfate administered before delivery may decrease incidence of cerebral palsy (CP) without affecting neonatal mortality.[80] A meta-analysis of trials calculated a RR of 0.69 (95% CI 0.55 to 0.91) with a number needed to treat to prevent one case of CP of 63 (95% CI 43 to 155).[81] Dosage regimes varied between individual studies; the regime used by Rouse et al is a 6-gram intravenous bolus followed by constant infusion of 2 grams per hour until delivery or for 12 hours maximum.[82]

If $MgSO_4$ is to be used for neuroprotection in PTL, physicians and hospitals should develop specific guidelines for use based on these studies.[80]

slide 21

slide 22

slide 23

slide 24

Table 10. **Pharmaceutical Agents for Tocolysis**

Drug (Class)	Dosage	Comment	Contraindications and Side Effects
Magnesium sulfate	4 to 6 gm bolus over 20 minutes, then 1 to 2 gm/hr (3 gm/hr maximum)	In widespread use in the United States, meta-analysis fails to demonstrate improvement in outcomes. Comparison studies demonstrate similar effectiveness to other agents in delay of delivery.	*Contraindication:* Myasthenia gravis *Maternal side effects:* Flushing, lethargy, headache, muscle weakness, diplopia, dry mouth, pulmonary edema, cardia arrest. Toxicity rare with serum level < 10 mg/dl. Respiratory depression and subsequent arrest can occur at levels > 10 to 12 mg/dl.[78] *Newborn side effects:* Lethargy, hypotonia, respiratory depression, demineralization with prolonged use.
Nifedipine (Calcium Channel Blocker)	30 mg oral loading dose, then 10 to 20 mg every four to six hrs	Nifedipine may offer the best outcomes of the tocolytic agents. May prolong pregnancy for seven days. Neonatal mortality not affected. Decreased incidence of neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage and jaundice.	*Contraindication:* Maternal hypotension *Maternal side effects:* Flushing, headache, dizziness, nausea, transient hypotension No fetal side effects noted.
Terbutaline (Betamimetic)	0.25 mg subcutaneously every 20 minutes for up to three doses	Betamimetic drugs may delay delivery for 48 hours but neonatal outcomes are variable and maternal side effects common. Terbutaline should not be used for more than 48 to 72 hours.	*Maternal contraindications:* Heart disease, poorly controlled diabetes, thyrotoxicosis *Maternal side effects:* - Cardiac arrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia - Hyperglycemia, hyperinsulinemia, hypokalemia, antidiuresis, altered thyroid function - Physiologic tremor, palpitations, nervousness, nausea/vomiting, fever, hallucinations *Fetal and neonatal side effects:* - Tachycardia, hypoglycemia, hypocalcemia, hyperbilirubinemia, hypotension, intraventricular hemorrhage
Indomethacin (Nonsteroidal anti-inflammatory drug)	Loading dose: 50 mg rectally or 50 to 100 mg orally Maintenance dose: 25 to 50 mg orally every four hours for 48 hours Total 24-hour dose should not be greater than 200 mg	NSAIDs theoretically intervene more proximally in the labor 'cascade' than the other agents. Efficacy appears similar to other agents. Maternal side effect profile is favorable. Other NSAIDs (sulindac, ketorolac) may be used.	*Contraindications:* Maternal renal or hepatic impairment, active peptic ulcer disease. Oligohydramnios *Maternal side effects:* Nausea, heartburn *Fetal side effects:* Constriction of the ductus arteriosus (not recommended after 32 weeks gestation), pulmonary hypertension, reversible decrease in renal function with olioghydramnios, intraventricular hemorrhage, hyperbilirubinemia, necrotizing enterocolitis May be optimal choice for tocolysis before 32 weeks' gestation

slides 25-27

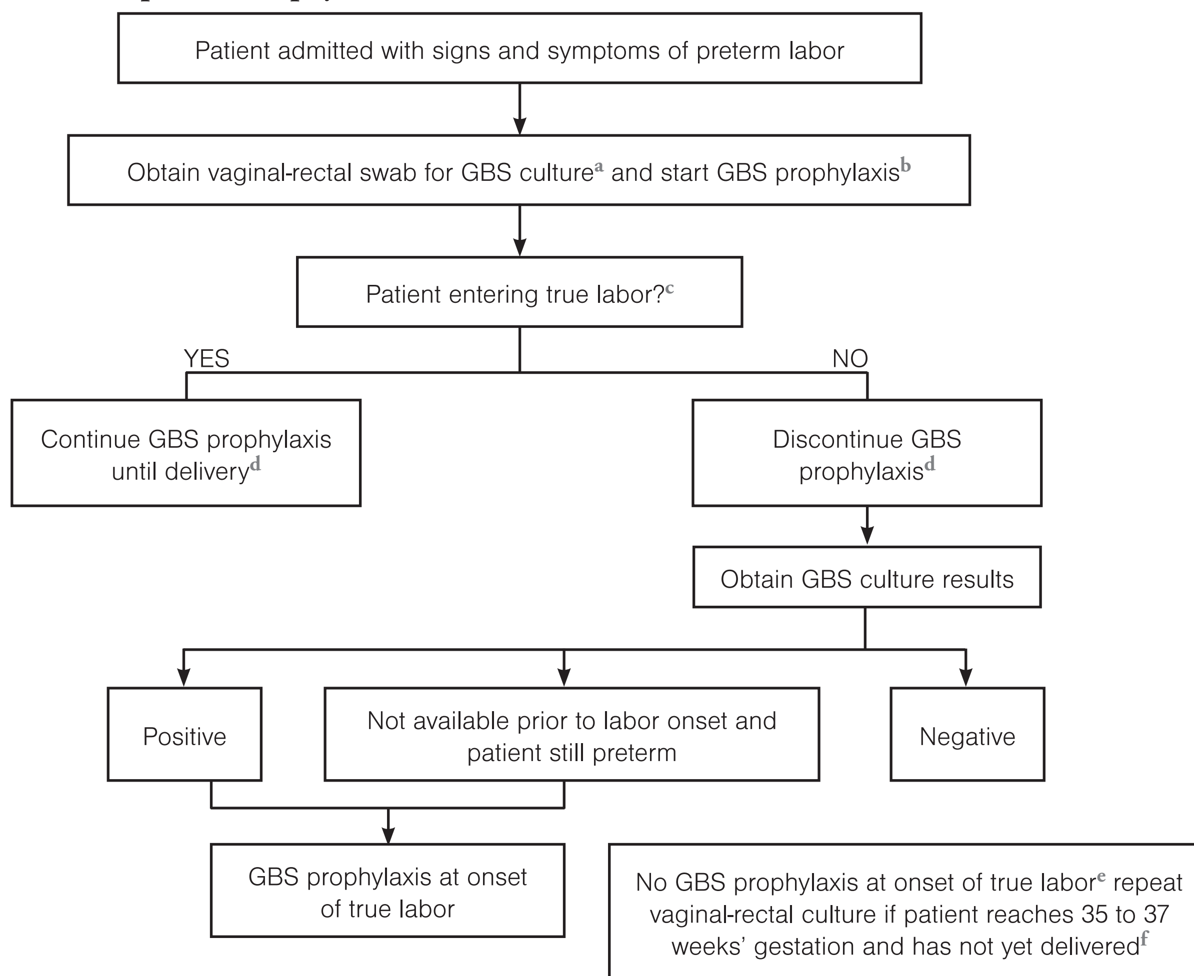
NEONATAL GROUP B STREPTOCOCCAL (GBS) PROPHYLAXIS

Given the current recommendation for universal prenatal screening at 35 to 37 weeks, most patients in preterm labor will not have culture results available. A GBS swab should be obtained for culture when women present with preterm labor or preterm premature rupture of membranes. Rapid tests for GBS colonization in women presenting with threatened PTL, but whose GBS status is unknown, are available;[83] however, the 2010 CDC guidelines recommend against using the current nucleic

acid amplification tests (NATT) in women under 37 weeks' gestation due to decreased sensitivity compared to culture. Intrapartum antibiotics should be used for prophylaxis until it is determined that the woman is not in true preterm labor, unless a negative GBS culture result becomes available.[84] Women who are allergic to penicillin may receive cefazolin unless the allergic response was anaphylaxis, angioedema, respiratory distress, or urticarial. Women with a history of these serious reactions should receive vancomycin unless sensitivity testing has demonstrated that the GBS isolate is susceptible to clindamycin and erythromycin. If sensitive to clindamycin and resistant to erythromycin, then testing for inducible resistance to clindamycin must be performed if clindamycin is to be used rather than vancomycin. CDC algorithms (Figures 4 and 5) for screening and GBS prophylaxis treatment of women with threatened preterm delivery, is presented below:

Figure 4. **Algorithm for Screening for Group B Steptococcal (GBS) Colonization and Use of Intrapartum Prophylaxis for Women With Preterm* (PTL)**[84]

slides 28,29



* *At < 37 weeks and 0 days' gestation.*

a *If patient has undergone vaginal-rectal GBS culture within the preceding five weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within five weeks was negative.*

b *See Table 11 for recommended antibiotic regimens.*

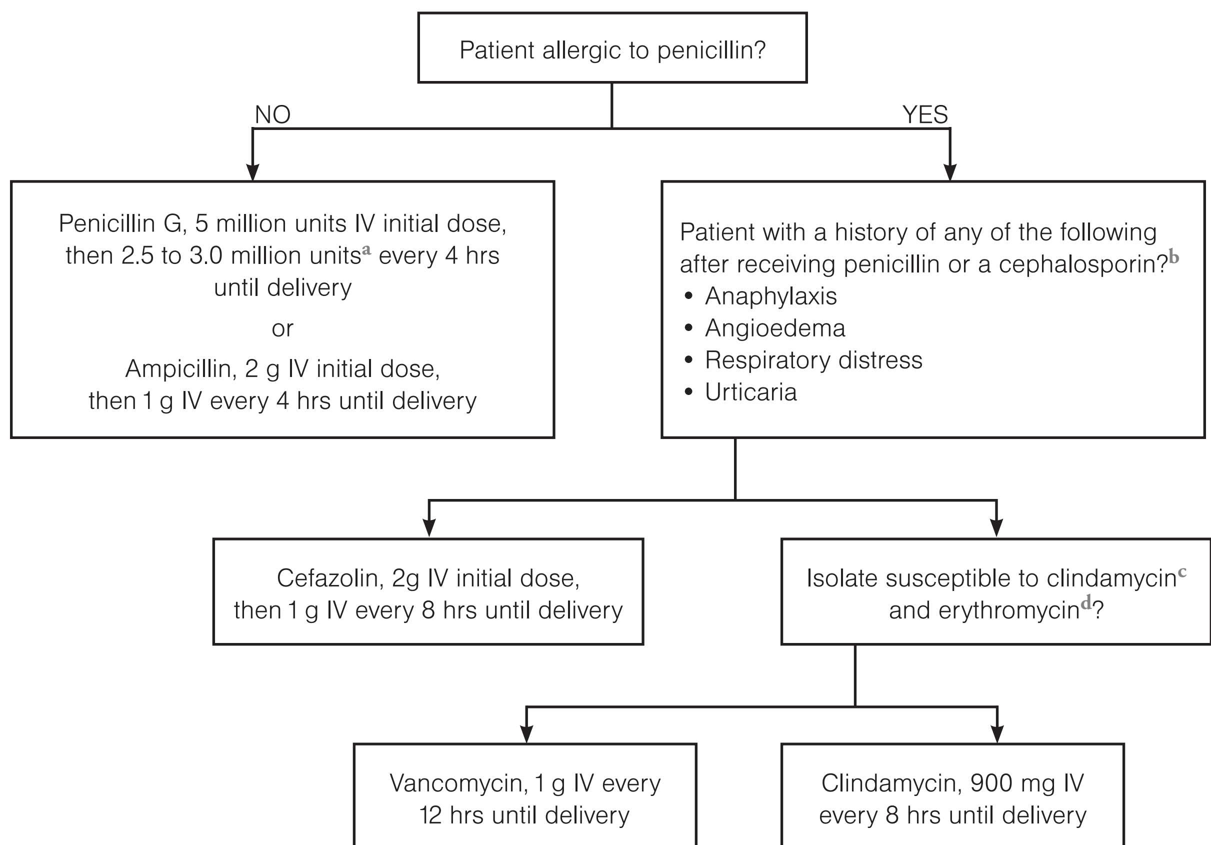
c *Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.*

d *If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis.*

e *Unless subsequent GBS culture prior to delivery is positive.*

f *A negative GBS screen is considered valid for five weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen > five weeks prior, she should be rescreened and managed according to this algorithm at that time.*

Figure 5. **Recommended Regimens for Intrapartum Antibiotic Prophylaxis for Prevention of Early-onset Group B Streptococcal (GBS) Disease**[84]



Abbreviation: IV = intravenously

* *Broader spectrum agents, including an agent active against GBS, might be necessary for treatment of chorioamnionitis.*

a *Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduct the need for pharmacies to specially prepare doses.*

b *Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis.*

c *If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 3) shold be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptability testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis.*

d *Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be usecd for GBS intrapartum prophylaxis instead of vancomycin.*

PRETERM PREMATURE RUPTURE OF THE FETAL MEMBRANES (PPROM)

Twenty-five to 30 percent of preterm deliveries are preceded by PPROM.[2] The biochemical events leading to PPROM appear to be different from those leading to PTL. Collagen fibers contribute to the tensile strength of the fetal membranes. Matrix metalloproteinase (a collagenase) activity is increased, possibly the result of infection or other inflammation, and may be the final common pathway leading to membrane rupture. In the context of placental abruption, thrombin may be involved as well.[85]

slide 30

The earlier in pregnancy PROM (and PTL in general) occurs, the more likely that it is associated with infection.[86] Risk factors for PPROM are similar to those for preterm labor with intact membranes.[50] Delivery is likely within a week of rupture. The earlier in pregnancy the rupture occurs, however, the greater the potential latency period. Clinically evident, intra-amniotic infection will develop in 13 to 60 percent of cases, the likelihood of which is increased by digital vaginal examination.[86,87] Principal threats to the fetus are complications of prematurity. Intrauterine complications include umbilical cord compression, abruption of the placenta, infection and pulmonary developmental abnormalities.[50] Infection may lead to maternal morbidity and likely plays a role in initiation of labor.

INITIAL EVALUATION OF THE PATIENT WITH SUSPECTED PPROM[88,89]

- Accurate dating is critical: Review dating criteria as management choices are determined by gestational age.
- Sterile speculum examination: If rupture of membranes is suspected, digital examination should be avoided as it shortens the latency period before onset of labor and increases the risk of infection. Diagnosis of rupture of membranes is discussed above. A sample of amniotic fluid may be obtained for fetal lung maturity evaluation if between 32 and 34 weeks (see below).
- Ultrasound evaluation: Oligohydramnios supports the diagnosis of membrane rupture. Oligohydramnios will also decrease the accuracy of fetal weight and gestational assessment. Low amniotic volume increases the likelihood of cord compression and other complications.
- Assessment of fetal lung maturity: Vaginal amniotic fluid may be tested for phosphatidyl glycerol, the presence of which indicates fetal lung maturity[90] between 32 and 34 weeks' gestation, although this is not commonly done. Amniocentesis allows collection of fluid for fetal pulmonary maturity testing as well as for evaluation of infection.[91]
- Screen for infection: Cervical cultures for sexually transmitted infections or vaginal/rectal culture for group B streptococcus may be obtained.
- Fetal monitoring: Electronic fetal heart rate and uterine contraction monitoring during initial assessment may identify cord compression and asymptomatic contractions.

MANAGEMENT OF PPROM

As in the case of premature labor with intact membranes, the management of PPROM necessitates a balance between the advantages of delaying delivery and risks of prolonging fetal exposure to a potentially hostile environment. Initial management is predicated on gestational age with the expected benefits of expectant management and administration of corticosteroids increasing for earlier gestational ages. Prolonging pregnancy after 34 weeks may result in poorer outcomes.[92]

slide 31

- Monitor for clinical infection: Maternal fever, uterine tenderness and fetal tachycardia are indicators of infection.
- Antepartum fetal testing: Non-stress testing is useful for detection of fetal heart rate decelerations which may occur due to umbilical cord compression in the setting of oligohydramnios. Biophysical profile testing has been used to predict chorioamnionitis, although daily testing is necessary.[93] Oligohydramnios (largest pocket <2 cm) indicates increased risk of infection.[93]
- Antibiotic therapy: At gestations between 24 and 32 weeks, treatment with antibiotics prolongs pregnancy, decreases fetal morbidity, decreases chorioamnionitis and maternal infection.[94] PPROM antibiotic regimens that include ampicillin 1 gram IV every six hours are adequate for GBS prophylaxis per CDC, despite the every six-hours dosing interval rather than the every four hours for routine GBS intrapartum prophylaxis.[84] The antibiotics and dosages used in a large National Institute of Child Health and Human Development trial are listed below.[95]

Table 11. **Antibiotic Therapy in PPROM**[95]

Antibiotic	Dosage
Initial therapy:	
Ampicillin	2 grams intravneously every six hours for 48 hours
Erythromycin	250 mg intravenously every six hours for 48 hours
Followed by:	
Amoxicillin	250 mg orally every eight hours for five days
Erythromycin base	333 mg orally every eight hours for five days

- Corticosteroids: Antenatal corticosteroid administration in the setting of PPROM reduces the risk of neonatal respiratory distress syndrome (RR 0.56; 95% CI 0.46 to 0.70), intraventricular hemorrhage (RR 0.47; 95% CI 0.31 to 0.70), and necrotizing enterocolitis (RR 0.21; 95% CI 0.05 to 0.82). There is a trend to decreased neonatal death. Incidence of maternal and neonatal infection is not increased.[96] The American College of Obstetricians and Gynecologists (ACOG) recommends treatment before 32 weeks. Efficacy of treatment from 32 to 33 weeks is reported as unclear but possibly beneficial in the setting of fetal pulmonary immaturity.[97] Corticosteroid dosages are listed above.
- Tocolysis: As opposed to antibiotic and corticosteroid treatment, tocolysis in the context of PPROM lacks evidence of benefit. Association of infection with onset of labor would be expected to be stronger in PPROM as opposed to PTL with intact membranes indicating circumspection in choosing tocolysis. ACOG has no recommendation regarding tocolysis in PPROM.[86]

GESTATIONAL AGE AND MANAGEMENT OF PPROM

slide 32

Greater than or equal to 34 weeks, electively induce labor: Incidence of RDS as well as composite morbidity in neonates delivered in the 34th week is no different from those in the 35th and 36th weeks.[92] Interventions such as corticosteroids and antibiotics are no longer indicated. At 34 weeks, elective induction of labor with PPROM reduces the incidence of chorioamnionitis and neonatal sepsis.[92]

Thirty-two to 33 weeks, induce if fetal lungs mature based on amniocentesis or vaginal pool sample. As with induction versus observation after 34 weeks, elective induction improves outcomes in pregnancies with evidence of fetal lung maturity. For those pregnancies without fetal lung maturity, management is less clear. Corticosteroid and antibiotic therapy are a consideration.[80,86,98]

Twenty-four to 32 weeks, administer antibiotics and corticosteroids, monitor for infection and other intrauterine fetal complications. If there is no evidence of fetal compromise and labor does not begin spontaneously, these pregnancies are managed expectantly until they reach 34 weeks.[50,86,91]

DELIVERY OF THE PRETERM INFANT

slide 33

Premature delivery at a facility with a high-volume level III Neonatal Intensive Care Unit (NICU) results in better neonatal outcomes.[99] If delivery is not imminent and level III services are unavailable, then maternal transfer is indicated. Using a proactive approach wherein very preterm infants (22 to 26 weeks' gestation) were delivered at a level III facility and antenatal steroids were delivered, one-year survival rates were 70 percent, ranging from 9.8 percent at 22 weeks to 85 percent at 26 weeks.[100] Fetuses at 22 to 25 weeks are considered at the cusp of viability and decisions for intervention with tocolysis, cesarean delivery for nonreassuring fetal heart tones, and neonatal intensive unit care requires careful consultation with parents and consideration of the specific risks and benefits. The National Institute of Child Health and Human Development (NICHD) has developed a web-based tool for describing outcomes of these neonates based on gestational age, weight, sex, and administration of antenatal corticosteroids. (http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm).

The preterm fetus is more susceptible to injury from acidosis and anoxia and therefore should be monitored continuously.[101] Neurologic immaturity of the fetus and effects of medications such as betamimetics complicate fetal heart rate monitoring. Malpresentations are more common at earlier gestations and should be anticipated.[102]

There is some retrospective evidence that elective cesarean delivery of extremely premature (22 to 31 weeks' gestation)[103] or very low birth weight (< 750 grams) infants[104] may improve some neonatal outcomes. The beneficial effect of elective cesarean delivery of these fetuses is not apparent, however, when applied to all deliveries at less than 37 weeks' gestation, while increasing maternal morbidity.[105] The lack of specificity in the diagnosis of true preterm labor results in the theoretical risk of surgical delivery of a patient not truly in preterm labor, an eventuality suggested in one of the trials.[105] For these reasons, cesarean delivery for the vertex preterm fetuses should be done for standard obstetric indications rather than for prematurity.[106]

There is no evidence that prophylactic episiotomy or forceps delivery improves neonatal outcome in preterm delivery.[106,107] Use of vacuum extraction is generally considered inappropriate before 34 weeks' gestation, due to the risk of intraventricular hemorrhage.[108] Umbilical cord blood acid-base studies should be considered following delivery given higher rates of cerebral palsy in preterm infants. The third stage of labor may be prolonged. Retained placenta is more common than with term pregnancies[109] and is best managed with uterine stimulants.

slide 34

PREMATURE RUPTURE OF MEMBRANES (PROM) AT TERM

Rupture of the membranes prior to the onset of labor occurs in 10 percent of pregnancies. Ninety percent of PROM occurs at greater than 37 weeks' gestation.[110] Diagnosis of ruptured membranes is discussed above. PROM at term confronts the clinician with several treatment decisions.

Positive amniotic fluid cultures for almost one-third of women presenting with PROM at term have been demonstrated, although only a small proportion will go on to develop clinical chorioamnionitis or endometritis.[111] Since maternal chlamydial and gonorrheal infections increase the risk for PROM, consider cervical cultures.[112] For women who are colonized, antimicrobial chemoprophylaxis for GBS is discussed above. If GBS status is unknown at time of presentation, intrapartum chemoprophylaxis should be administered to women with duration of membrane rupture > 18 hours, or temperature ≥ 100.4°F (≥ 38°C).[84] As in PPROM, digital cervical examinations are associated with increased incidence of chorioamnionitis[113] and neonatal infection.[114]

PLANNED DELIVERY VS. EXPECTANT MANAGEMENT IN PATIENTS NOT IN LABOR

Labor induction with oxytocin is recommended when term PROM occurs and labor does not follow.[115] Despite this recommendation, some women may prefer expectant management. The Cochrane review on term PROM concludes that since the difference in outcomes based on management plan is small, women should receive information to make an informed choice.[116] Elective induction of labor does not reduce the incidence of neonatal infection overall, but does decrease admissions to newborn intensive care (RR 0.72; CI 0.56 to 0.97). Mothers are less likely to develop chorioamnionitis (RR 0.74; CI 0.56 to 0.97) or endometritis (RR 0.30; CI 0.12 to 0.74).[116] Actively managed GBS-colonized mothers, however, deliver neonates with significantly lower rates of infection (2.5 percent) than those who are expectantly managed (eight percent).[117] Elective induction does not increase the rate of cesarean deliveries in the setting of term PROM.[118] Oral and vaginal misoprostol as well as PGE2 have been used for elective induction of labor in the setting of term PROM but offer no advantage over oxytocin.[119]

CONCLUSION

slides 35,36

It is possible to identify some patients at high risk for PTD, and a subset of these may benefit from preventive interventions such as antenatal progesterone. In the triage of patients presenting with preterm contractions, it is possible to stratify their risk of subsequent preterm delivery. The major role of tocolysis is delay of delivery for the 48 hours necessary for the full therapeutic effect of antenatal steroids. Management of PPROM presents its own set of challenges and is primarily based on gestational age. Antenatal steroids and antibiotics are useful in some cases. Although term PROM is often managed expectantly, there is little research to support that approach and some to support immediate induction of labor or after a short interval of expectant management. Preterm labor remains an area of intense research activity and therapeutic evolution. Addressing the role of infection in PTL is a particular area of interest.

SUMMARY

Category A

Antenatal progesterone supplementation decreases the incidence of preterm delivery in high-risk patients.[32]

Administration of corticosteroids in women with preterm labor between 26 and 34 weeks' gestation reduces the incidence of neonatal death, respiratory distress syndrome, and intraventricular hemorrhage.[63]

In symptomatic patients, calcium channel blockers reduce the risk of delivery within seven days and before 34 weeks' gestation. Calcium channel blockers are better tolerated than betamimetics.[69]

In symptomatic patients, betamimetics decrease the risk of delivery within 48 hours. They are associated with significant adverse effects, and should not be used for more than 48 to 72 hours.[71]

Category C

If delivery is not imminent, maternal transfer to a facility with a level III neonatal intensive care unit is indicated.[99,100]

REFERENCES

1 Martin JA, Hamilton BE, Sutton PD, et al. Births: Final data for 2008. *Nat Vital Stat Rep.* 2010;59:1.

2 Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008;371(9606):75-84.

3 Sunderam S, Chang J, Flowers L, et al. Assisted reproductive technology surveillance – 2006. *MMWR.* 2009;58(SS05):1-25.

4 Heron M, Hoyert DL, Murphy SL, et al. Deaths: final data for 2006. *Nat Vital Stat Rep.* 2009;57:1-134.

5 Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. *Semin Perinatol.* 2006;30(1):28-33.

6 Ananth CV, Joseph KS, Oyelese Y, et al. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. *Obstet Gynecol.* 2005;105:1084-1091.

7 Mercer B, Milluzzi C, Collin M. Periviable birth at 20-26 weeks of gestation: proximate causes, previous obstetrical history and recurrence risk. *Am J Obstet Gynecol.* 2005;193(3 Pt 2):1175-11

8 Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse pregnancy outcomes, a meta-analysis. *JAMA.* 2006;295:1809-1823.

9 Moutquin JM. Classification and heterogeneity of preterm birth. BJOG. 2003;110(Suppl 20):30-33.

10 Schieve LA, Rasmussen SA, Buck GM, Schendel DE, Reynolds MA, Wright VC. Are children born after assisted reproductive technology at increased risk for adverse health outcomes? *Obstet Gynecol.* 2004;103(6):1154-1163.

11 Rodrigues T, Rocha L, Barros H. Physical abuse during pregnancy and preterm delivery. *Am J Obstet Gynecol.* 2008;198(2):171.e1-6.

12 The Role of Environmental Toxicants in Preterm Birth. Behrman RE, Butler AS (eds). *Preterm birth: causes consequences and prevention.* Washington, DC: The National Academies Press; 2007. 229-254.

13 Behrman RE, Butler AS (eds). Preterm birth: causes consequences and prevention. Washington, DC: The National Academies Press; 2007. 91.

14 Cnattingius S, Granath F, Petersson G, et al. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. *N Engl J Med.* 1999;341(13):943-948.

15 Sadler L, Saftlas A, Wang W, et al. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA.* 2004;291(17):2100-2106.

16 Mercer BM, Golderberg RL, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol.* 1999;181(5 Pt 1):1216-1221.

17 Adams MM, Elam-Evans LD, Wilson HG, et al. Rates of and factors associated with recurrence of preterm delivery. *JAMA.* 2000;283(12):1591-1596.

18 Ananth CV, Vintzileos AM. Medically indicated preterm birth: recognizing the importance of the problem. *Clin Perinatol.* 2008;35(1):53-67.

19 Stock S, Norman J. Preterm and term labour in multiple pregnancies. *Semin Fetal Neonatal Med.* 2010;15(6):336-341.

20 Heron JA, Hamilton BE, Sutton PD, et al. Births: final data for 2002. *National Vital Statistics Reports.* 2003:52:1-114.

21 Newton E. Preterm labor, preterm premature rupture of the membranes, and chorioamnionitis. *Clin Perinatol.* 2005;32(3):571-600.

22 Leitich H, Bodner-Adler B, Brunbauer M, et al. Bacterial vaginosis as a risk factor for preterm delivery: a meta-analysis. *Am J Obstet Gynecol.* 2003;189(1):139-147.

23 Small FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2007(2):CD000490.

24 Offenbacher S, Boggess KA, Murtha A, et al. Progressive periodontal disease and the risk of very preterm delivery. *Obstet Gynecol.* 2006;107(1):29-36.

25 Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. *BJOG.* 2006;113 (Suppl 3):17-42.

26 Iams JD, Newman RB, Thom EA, et al. Frequency of uterine contractions and the risk of spontaneous preterm delivery. *N Engl J Med.* 2002;346(4):250-255.

27 Iams JD. Prediction and early detection of preterm labor. *Obstet Gynecol.* 2003;101(2):402-412.

28 Iams JD, Romero R, Creasy RK. Preterm labor and birth. Creasy RK, Resnik R, Iams JD, Lockwood CJ, Moore TR (eds). *Creasy and Resnik's Maternal-Fetal Medicine, Principles and Practice, Sixth Edition.* Philadelphia, PA: Saunders; 2009. 559.

29 Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. *N Engl J Med.* 1996;334(9):567-572.

30 Iams JD, Romero R, Culhane JF, et al. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet.* 2008;371(9607):164-175.

31 O'Brien JM, Adair CD, Lewis DF et al. Progesterone vaginal gel for the reduction of recurrent preterm birth; primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol.* 2007;30(5):687-696.

32 Dodd JM, Flenady V, Cincotta R, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev.* 2006(1):CD004947.

33 Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha hydroxyprogesterone caproate. *N Engl J Med.* 2003;348(24):2379-2385.

34 Fonseca EB, Celic E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med.* 2007;357(5):462-469.

35 Rouse DJ, Caritis SN, Peasceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med.* 2007;357(5):454-461.

36 Tita ATN, Rouse DJ. Progesterone for preterm birth: an evolving intervention. *Am J Obstet Gynecol.* 2009;200(3):219-224.

37 Fonseca EB, Bittar RE, Carvalho MHB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol.* 2003;188(2):419-424.

38 Society for Maternal Fetal Medicine Publications Committee. ACOG Committee Opinion No. 419 October 2008. Use of progesterone to reduce preterm birth: ACOG committee opinion No.419. *Obstet Gynecol.* 2008;112(4):963.

39 Lamont RF, Duncan SLB, Mandal D, et al. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. *Obstet Gynecol.* 2003;101(3):516-522.

40 Ugwumadu A, Manyonda I, Reid F, et al. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomized trial. *Lancet.* 2003;361(9362):983-988.

41 Kiss H, Petricevic L, Husslein P. Prospective randomized controlled trial of an infection screening programme to reduce the rate of preterm delivery. *BMJ.* 2004;329(7462):371-374.

42 US Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2008;148(3):214-219.

43 Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am J Med.* 1983;74(1):14-22.

44 Workowski KA, Berman SM. Sexually transmitted diseases guidelines, 2006. *MMWR Recomm Rep.* 2006;55(RR11):1-94.

45 Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. *Cochrane Database Syst Rev.* 2003(1):CD003253.

46 Lumley J, Oliver SS, Chamberlain C, et al. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev.* 2004(4):CD001055.

47 Dyson DC, Danbe KH, Bamber JA, et al. Monitoring women at risk for preterm birth. *N Engl J Med.* 1998;338(1):15-19.

48 Michalowicz BS, Hodges JS, Di Angelis AJ, et al. Treatment of periodontal diseases and the risk of preterm birth. *N Engl J Med.* 2006;355(18):1885-1894.

49 Kramer MS, Kakuma R. Energy and protein intake in pregnancy. *Cochrane Database Syst Rev.* 2003(4):CD000032.

50 Mercer BM. Preterm premature rupture of the membranes. *Obstet Gynecol.* 2003;101(1):178-193.

51 Bennett SL, Cullen JB, Sherer DM, et al. The ferning and nitrazine tests of amniotic fluid between 12 and 41 weeks gestation. *Am J Perinatol.* 1993;10(2):101-104.

52 Cousins LM; Smok DP; Lovett SM; Poeltler DM. AmniSure placental alpha microglobulin-1 rapid immunoassay versus standard diagnostic methods for detection of rupture of membranes. *Am J Perinatol.* 2005;22(6):317-320.

53 Lee SE, Park JS, Norwitz ER, et al. Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes. *Obstet Gynecol.* 2007;109(3):634-640.

54 Ratcliffe SD. Chorioamnionitis. Ratcliffe SD, Baxley EG, Cline MK, Sakornbut EL (eds). *Family Practice Obstetrics.* Philadelphia, PA: Elsevier, 2008. 448-457.

55 ACOG Committee on Practice Bulletins. American College of Obstetricians and Gynecologists. Clinical management guidelines for obstetrician-gynecologist. No. 43, May 2003. Management of preterm labor. *Obstet Gynecol.* 2003;101(5 Pt 1): 1039-1047.

56 McPheeters ML, Miller WC, Nartmann KE, et al. The epidemiology of threatened preterm labor: a prospective cohort study. *Am J Obstet Gynecol.* 2005;192(4):1329-1330.

57 Guinn DA, Goepfert AR, Owen J, et al. Management options in women with preterm uterine contractions: a randomized clinical trial. *Am J Obstet Gynecol.* 1997;177(4):814-818.

58 Honest H, Bachmann LM, Gupta JK, et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review. *BMJ.* 2002;325(7359):301.

59 Ramsey PS, Andrews WW. Biochemical predictors of preterm labor: fetal fibronectin and salivary estriol. *Clin Perinatol.* 2003;30(4):701-733.

60 Tsoi E, Fuchs IB, Rane S, et al. Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes. *Ultrasound Obstet Gynecol.* 2005; 25(4):353-356.

61 Owen J. Evaluation of the cervix by ultrasound for the prediction of preterm birth. *Clin Perinatol.* 2003;30(4):735-755.

62 Gomez R, Romero R, Medina L, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. *Am J Obstet Gynecol.* 2005;192(2):350-359.

63 Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2006(3):CD004454.

64 ACOG Committee Opinion No. 402. Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2008;111(3):805-807.

65 National Institutes of Health Consensus Development Panel. Antenatal corticosteroids revisited: repeat courses - National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. *Obstet Gynecol.* 2001;98(1):144-150.

66 Garite TJ, Kurtzman J, Maurel K, et al. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol.* 2009;200(3):248.e1-9.

67 Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antennal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. *JAMA.* 2001;286(13):1581-1587.

68 Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med.* 2007;357(12):1190-1198.

69 King JF, Flenady V, Papatsonis D, et al. Calcium channel blockers for inhibiting preterm labour. *Cochrane Database Syst Rev.* 2003(1): CD002255.

70 Naik Gaunekar N, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. *Cochrane Database Syst Rev.* 2004(3): CD004071.

71 Anotayanonth S, Subhedar NV, Neilson JP, et al. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev.* 2004(4):CD004352.

72 King JF, Flenady V, Cole S, et al. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev.* 2005(2):CD001992.

73 Norton ME, Merrill J, Cooper B, et al. Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med.* 1993;329(22):1602-1607.

74 Loe SM, Sanchez-Ramos L, Kaunitz AM. Assessing the neonatal safety of indomethacin tocolysis. *Obstet Gynecol.* 2005:106(1):173-179.

75 Haas DM, Imperiale TF, Kirkpatrick PR, et al. Tocolytic therapy, a meta-analysis and decision analysis. *Obstet Gynecol.* 2009;113(3):585-594.

76 Simhan H, Caritis SN. Prevention of preterm delivery. *N Engl J Med.* 2007;357(5):477-487.

77 Fox NS, Gelber SE, Kalish R, et al. Contemporary practice patterns and beliefs regarding tocolysis among US maternal-fetal medicine specialists. *Obstet Gynecol.* 2008;112(1):42-47.

78 Mercer BM, Merlino AA. Magnesium sulfate for preterm labor and preterm birth. *Obstet Gynecol.* 2009;114(3):650-668.

79 Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev.* 2002(4):CD001060.

80 American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol.* 2010:115(3):669-671.

81 Doyle LW, Crowther CA, Middleton P, et al. Antenatal magnesium sulfate and neurologic outcome in preterm infants, a systematic review. *Obstet Gynecol.* 2009;113(6):1327-1333.

82 Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med.* 2008;(9)359:895-905.

83 Honest H, Sharma S, Khan KS. Rapid tests for group B Streptococcus colonization in laboring women: a systematic review. *Pediatrics.* 2006;117(4):1055-1066.

84 Centers for Disease Control and Prevention. Prevention of perinatal group B Streptococcal disease revised guidelines from CDC, 2010. *MMWR Recomm Rep.* 2010;59(RR-10):1-36.

85 Thomson A, Norman J. Biology of preterm labour. Norman J, Greer I (eds). *Preterm Labour, managing risk in clinical practice.* Cambridge, UK: Cambridge University Press; 2005. 26-75.

86 ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin No. 80: premature rupture of membranes. Clinical management guidelines for obstetricians-gynecologists. *Obstet Gynecol.* 2007;109(4):1007-1019.

87 Alexander JM, Mercer BM, Miodovnik M, et al. The impact of digital cervical examination on expectantly managed preterm rupture of membranes. *Am J Obstet Gynecol.* 2000;183:1003-1007.

88 Combs CA, McCune M, Clark R, et al. Aggressive tocolysis does not prolong pregnancy or reduce neonatal morbidity after preterm premature rupture of the membranes. *Am J Obstet Gynecol.* 2004;190(6):1723-1731.

89 Mercer BM, Crocker LG, Boe NM, et al. Induction versus expectant management in premature rupture of the membranes with mature amniotic fluid at 32 to 36 weeks: a randomized trial. *Am J Obstet Gynecol.* 1993;169(4):775-782.

90 Lewis DF, Futayyeh S, Towers CV, et al. Preterm delivery from 34 to 37 weeks of gestation: is respiratory distress syndrome a problem? *Am J Obstet Gynecol.* 1996;174(2):525-528.

91 Simhan HN, Canavan TP. Preterm premature rupture of membranes: diagnosis, evaluation and management strategies. *BJOG.* 2005;112(Suppl 1):32-37.

92 Naef RW, Allbert JR, Ross EL, et al. Premature rupture of membranes at 34-37 weeks' gestation: aggressive versus conservative management. *Am J Obstet Gynecol.* 1998;178(1 Pt 1):126-130.

93 Hanley ML, Vintzileos AM. Biophysical testing in premature rupture of the membranes. *Sem Perinatol.* 1996;20(5):418-425.

94 Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. *Obstet Gynecol.* 2004;104(5 Pt 1):1051-1057.

95 Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm rupture of the membranes: a randomized trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA.* 1997;278(12):989-995.

96 Harding JE, Pang J-M, Knight DM, et al. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? *Am J Obstet Gynecol.* 2001;184(2):131-139.

97 American College of Obstetricians and Gynecologists Committee on Obstetric Practice. ACOG Committee Opinion No. 402. Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol.* 2008;111:805-807.

98 Medina TM, Hill DA. Preterm Premature Rupture of Membranes: Diagnosis and Management. *Am Fam Physician.* 2006;73(4):659-664.

99 Warner B, Musial J, Chenier T, et al. The effect of birth hospital type on the outcome of very low birth weight infants. *Pediatrics.* 2004;113(1 Pt 1):35-41.

100 EXPRESS Group, Fellman V, Hellstrom-Westas L, Norman M, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA.* 2009;301(21):2225-2233.

101 Westgren LM, Malcus P, Svenningsen N. Intrauterine asphyxia and long-term outcome in preterm fetuses. *Obstet Gynecol.* 1986;67(4):512-516.

102 Bottoms S. Delivery of the premature infant. *Clin Obstet Gynecol.* 1995;38(4):780-789.

103 Mallow MH. Impact of cesarean section on neonatal mortality rates among very preterm infants in the United States, 2000-2003. *Pediatrics.* 2008;122(2):285-292.

104 Deulofeut R, Sola A, Lee B, et al. The impact of vaginal delivery in premature infants weighing less than 1,251 grams. *Obstet Gynecol.* 2005;105(3):525-531.

105 Riskin A, Riskin-Mashiah S, Lusky A, et al. The relationship between delivery mode and mortality in very low birthweight singleton vertex-presenting infants. *BJOG.* 2004;111(12):1365-1371.

106 Goldenberg RL. The management of preterm labor. *Obstet Gynecol.* 2002;100(5 Pt 1):1020-1037.

107 Platek D, Chazotte C, Schulman M. Episiotomy does not protect against intraventricular hemorrhage in the very-low-birth-weight neonate. *Am J Obstet Gynecol.* 1993;168:371-376.

108 American College of Obstetricians and Gynecologists. Operative vaginal delivery. Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet.* 2001;74(1): 69-76.

109 Romero R, Hsu YC, Athanassiadis AP, et al. Preterm delivery: a risk factor for retained placenta. *Am J Obstet Gynecol.* 1990;163(3):823-825.

110 Naylor CS, Gregory K, Hobel C. Premature rupture of the membranes: an evidence-based approach to clinical care. *Am J Perinatol.* 2001;18:397-413.

111 Romero R, Mazor M, Morrotti R, et al. Infection and labor. VII. Microbial invasion of the amniotic cavity in spontaneous rupture of membranes at term. *Am J Obstet Gynecol.* 1992;166(1 Pt 1):129-133.

112 Ekwo ER, Gosselingk CA, Woolson R, et al. Risks for premature rupture of amniotic membranes. *Int J Epidemiol.* 1993;22(3):495-503.

113 Seaward PG, Hannah ME, Myhr TL, et al. International multicentre term PROM study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. Preterm rupture of the membranes. *Am J Obstet Gynecol.* 1998;179(3 Pt 1):635-639.

114 Seaward PG, Hannah ME, Myhr T, et al. International multicentre term prelabor rupture of membranes study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. *Am J Obstet Gynecol.* 1997;177(5):1024-1029.

115 American College of Obstetricians and Gynecologists. Premature Rupture of Membranes. ACOG Practice Bulletin No. 80. *Obstet Gynecol.* 2007;109:1007-1019.

116 Dare MR, Middleton P, Crowther CA, et al. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). *Cochrane Database Syst Rev.* 2006(1):CD005302.

117 Hannah ME, Ohlsson A, Wang EEL, et al. Maternal colonization with group B Streptococcus and prelabor rupture of membranes at term: the role of induction of labor. TermPROM Study Group. *Am J Obstet Gynecol.* 1997;177(4):780-785.

118 Peleg D, Hannah ME, Hodnett ED, et al. Predictors of cesarean delivery after prelabor rupture of membranes at term. *Obstet Gynecol.* 1999;93(6):1031-1035.

119 Mozurkewich EL, Wolf FM. Premature rupture of membranes at term: a meta-analysis of three management schemes. *Obstet Gynecol.* 1997;89(6):1035-1043.